Remarks

I. Status of Claims

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendments, claims 122-157 are pending in the application, with claims 122 and 141 being the independent claims. Claims 1-121 are canceled without prejudice or disclaimer of the subject matter therein, and new claims 122-159 are sought to be added. Support for the new claims can be found throughout the specification. For example, support for claims 122 and 141 can be found at page 6, lines 1-24 and page 10, lines 7-15. Support for claims 123 and 124 can be found at page 3, lines 7-33. Support for claims 125-132 and 142-149 can be found at page 7, line 30 - page 8, line 7, page 10, lines 16-24, and page 12, lines 11-21. Support for claims 133-140 and 150-157 can be found at page 8, lines 8-26 and page 12, line 22 - page 14, line 28. These changes are believed to introduce no new matter, and their entry is respectfully requested.

II. Amendments to the Specification

The Examiner requires that the title of the present application be amended to "the method of producing a concentrated anti-CD-20 antibody preparation." Applicants have amended the title as suggested. Applicants also amended the cross-reference to the related applications to correct the priority chain. Therefore, the amendments do not introduce new matter, and the objection should be withdrawn.

III. Summary of the Invention

The present invention relates to a method of conditioning an initial antibody preparation prior to a membrane filtration step to improve stability and reduce viscosity of the concentrated antibody at the post-membrane filtration stage. More specifically, Figures 5-7 and Tables I-II show that the initial antibody preparations buffered with 20 mM acetate or histidine improve filtration flow rate or decrease turbidity and viscosity of the concentrated antibody after a membrane filtration step, compared to the initial antibody preparation buffered with 20 mM citrate. *See also* at the Specification at page 22, line 16 to page 24, line 2.

IV. The Rejection Under 35 U.S.C. § 103(a) is Traversed.

Claims 22-32, 34-40, 42-52, 54-60, 62-72, and 74-80 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Lam *et al.*, U.S. Patent No. 6,171,586 B1 ("Lam"), filed June 13, 1997 and issued January 9, 2001, in view of Relton, U.S. Patent No. 6,252,055 B1 ("Relton"), filed November 12, 1998 and issued June 26, 2001. Claims 22, 41-42, 61-62, and 81 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Lam in view of Relton and Maloney *et al., Blood* 90(6): 2188-2195 (1997) ("Maloney"). Claims 22, 31-33, 42, 51-53, 62, and 71-73 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Lam in view of Relton and Newman *et al.*, U.S. Patent No. 5,658,570 B1, filed January 25, 1995 and issued August 19, 1999 ("Newman").

More specifically, the Examiner asserts that a person of ordinary skill in the art would have been "motivated to and had a reasonable expectation of success to have produced [*sic*] a method for producing a concentrated anti-CD20 antibody preparation ... because Lam et al

teach the preparation of anti-CD20 antibody compositions ... comprising an anti-CD20 ... antibody in 5mM to 30mM, or 10mM acetate or histidine buffer in the pH range of 4.5 to 6.0 ... and Relton et al teach ... filtering the antibody preparation ... using ultrafiltration ...." Office Action at pages 5-6. The Examiner also alleges that Moloney and Newman further teach the specific antibodies used for the claimed invention. *See* Office Action at pages 10-11. Applicants respectfully disagree.

Not in acquiescence with the Examiner's rejection, but to facilitate prosecution of this application, Applicants canceled all claims and submitted new claims. The newly submitted claims now recite a method of producing concentrated anti-CD20 antibodies comprising (a) providing an initial antibody preparation, which comprises or consists essentially of an aqueous solution of anti-CD20 antibodies and histidine or acetate buffer, wherein the concentration of the histidine or acetate buffer is about 2mM to about 48mM, and (b) filtering the initial antibody preparation using a membrane filtration that removes water and buffer but not antibodies. Insofar as the rejection applies to the newly submitted claims, Applicants respectfully traverse.

The factors to be considered under 35 U.S.C. § 103(a) are the scope and content of the prior art; the differences between the prior art and the claims at issue; and the level of ordinary skill in the pertinent art. *See Graham v. John Deere*, 86 S.Ct. 684 (1966); M.P.E.P. §2141; *KSR International Co v. Teleflex Inc.*, 127 S.Ct. 1727 (2007). The Office published Examination Guidelines to aid Examiners in formulating obviousness rejections. *See* Examination Guidelines for Determining Obviousness under 35 U.S.C. § 103 in view of the Supreme Court decision in *KSR International v. Teleflex Inc.* Fed. Reg. Vol. 72, pp. 57526 to 57535 (October 10, 2007), hereinafter "the Examination Guidelines." Seven rationales are

suggested by which obviousness may be found, *e.g.*, by combining elements in the art or substituting one known element for another. As a common thread through all the rationales, the Examiner must establish on the record that a person of ordinary skill in the art would have recognized that the results of the combination or substitution were *predictable*. *Id.*, *e.g.*, at 57529.

Applicants assert that considering Lam, Relton, Maloney, and/or Newton as a whole, one of ordinary skill in the art would not have arrived at Applicants' claimed invention with any sort of predictability. Also, the superior properties of the claimed invention overcome a *prima facie* case of obviousness, if any.

First, Lam does not describe a method of improving stability and/or viscosity of "post-filtration" antibodies by pre-conditioning an initial antibody preparation with acetate or histidine buffer. While Lam discloses a *stable* final pharmaceutical formulation comprising 10 mM acetate or histidine, a person of ordinary skill in the art would not have been motivated from Lam to add a low concentration of acetate or histidine buffer to an initial antibody concentration for the purpose of improving the antibody's properties after membrane filtration. In fact, as acknowledged by the Examiner, Lam does not even disclose a membrane filtration step. Thus, a person of ordinary skill in the art would not have been motivated to further subject Lam's stable final formulation to a membrane filtration step that removes water and buffer. Instead, a skilled artisan would have expected that a further membrane filtration step would remove the carefully added ingredients from Lam's final formulation and therefore disturb its stability. *See* Col. 22, lines 18-59.

Relton does not cure the deficiencies of Lam. It is true that Relton discloses subjecting an antibody preparation to a membrane filtration step. However, like Lam, Relton

also failed to recognize the importance of using acetate or histidine to buffer the initial antibody preparation prior to the membrane filtration step. Indeed, the initial antibody preparations described in Relton contain 50 mM or higher *citrate* buffer as a conventional preparation method. *See* Relton at col. 9, lines 25-34. (emphasis added). In sum, when taken together, one of ordinary skill in the art would have been motivated to buffer an initial antibody preparation with a citrate buffer and subject the preparation to membrane filtration (as taught by Relton), followed by preparing a final antibody formulation with histidine or acetate (as taught by Lam).

Accordingly, Applicants submit that the combination of Lam and Relton does not arrive at the presently claimed invention, which requires acetate or histidine buffer in the initial antibody preparation, followed by a membrane filtration step.

Furthermore, neither Maloney nor Newman cures the deficiencies of Lam and Relton. As acknowledged by the Examiner, Maloney merely discloses administrating anti-CD20 antibody to treat non-Hodgkin's lymphomas. Newman discloses chimeric anti-CD20 antibodies comprising the variable regions of Old World monkeys and human constant regions.

Therefore, none of the cited references predict or suggest that the acetate or histidine buffer at the concentration from about 2 mM to about 48 mM, compared to the citrate buffer, would improve stability and viscosity of concentrated antibodies after a membrane filtration. Accordingly, the Examiner failed to establish a *prima facie* case of obviousness.

Even assuming, *arguendo*, that the Examiner has established a *prima facie* case of obviousness, Applicants submit that the superior properties of the present invention clearly rebut any such case.

A determination of obviousness under 35 U.S.C. § 103 requires an evaluation of any evidence of secondary considerations, including superior results. *Graham v. John Deere,* 383 U.S. 1 (1966); MPEP 2141, p. 2100-113. "Evidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a *prima facie* case of obviousness." *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987).

As discussed above, the claimed methods clearly display superior properties to the known conventional methods. For example, Figure 5 describes that an acetate or histidine buffer improves filtration flow rate compared to a citrate buffer. *See also* at the Specification at page 21, line 30 to page 22, line 15. More specifically, Table I indicates that "antibody solutions formulated with citrate took about 30% more time to concentrate than those formulated with acetate, and about 50% more time than those formulated with histidine." The Specification at page 22, lines 8-15. Figures 6 and 7 and Table II show that the acetate or histidine buffer decreases turbidity and viscosity of the concentrated antibody, respectively, compared to the citrate buffer. *See also* at the Specification at page 22, line 16 to page 24, line 2. Therefore, the properties of the claimed invention overcome any *prima facie* case of obviousness. Accordingly, Applicants believe that the rejection under 35 U.S.C. § 103(a), if applied to the newly submitted claims, have been properly traversed, fully accommodated or rendered moot, and respectfully request that the rejection be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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